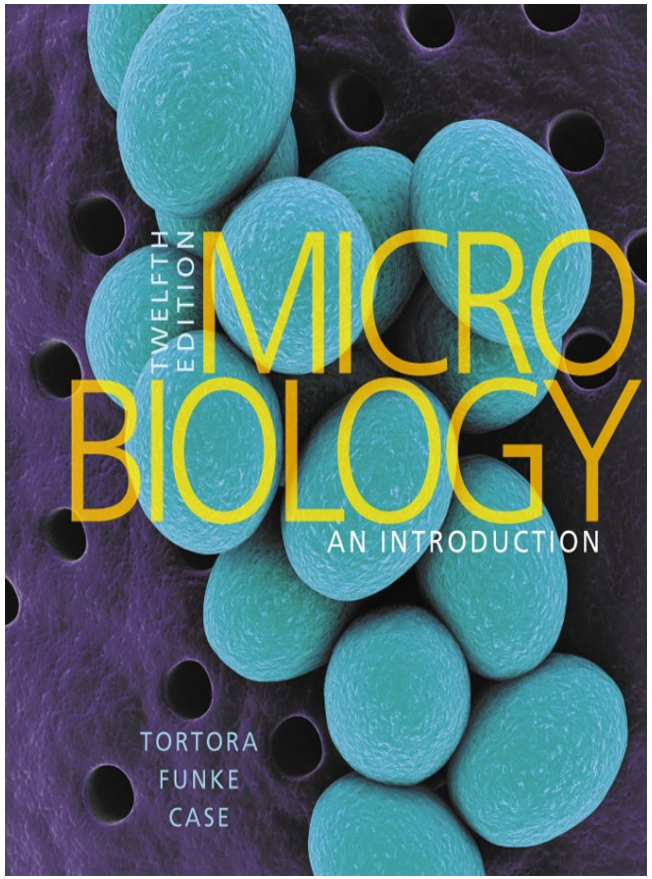
# Microbiology an Introduction

Twelfth Edition

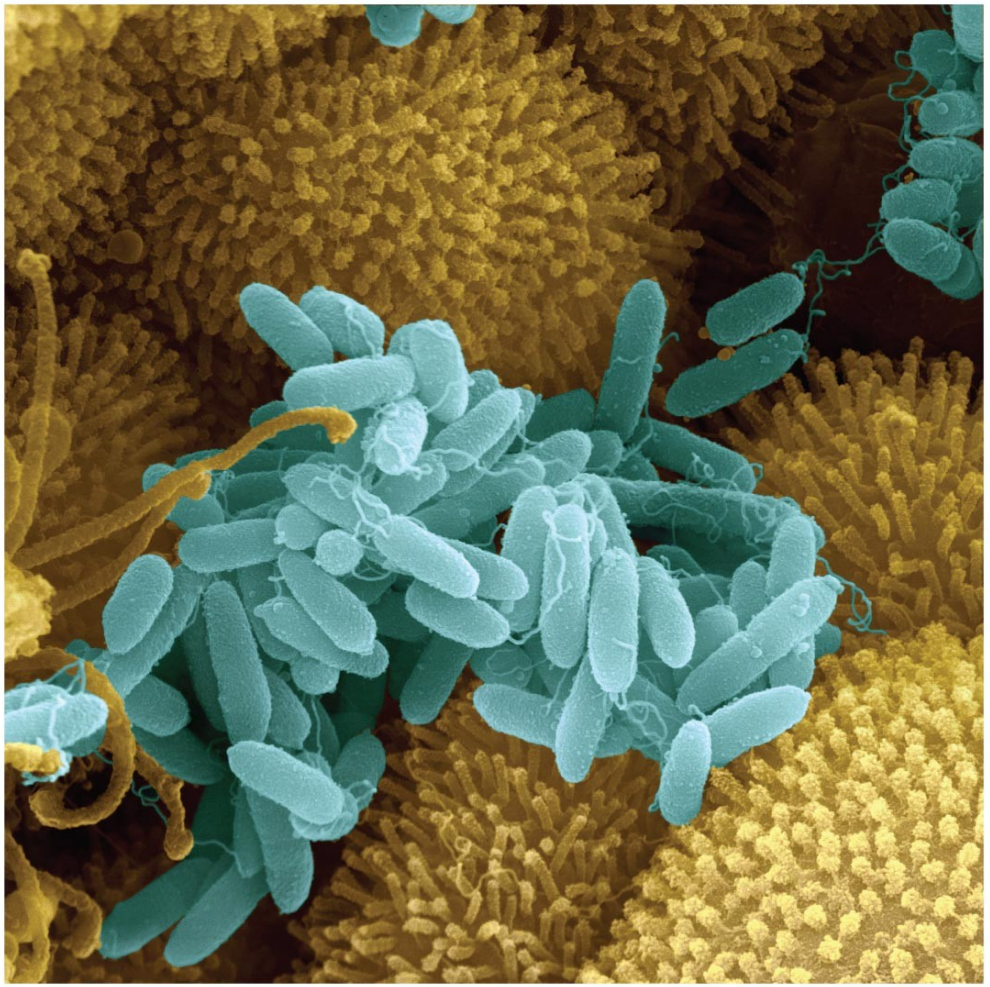



## Chapter 20

Antimicrobial Drugs

Pearson

# Pseudomonas Aeruginosa (Blue)



# The History of Chemotherapy (1 of 3)

## Learning Objectives

20-1 Identify the contributions of Paul Ehrlich and Alexander Fleming to chemotherapy.

20-2 Name the microbes that produce most antibiotics.

# The History of Chemotherapy (2 of 3)

- **Selective toxicity:** selectively finding and destroying pathogens without damaging the host
- **Chemotherapy:** the use of chemicals to treat a disease
- **Antibiotic:** a substance produced by a microbe that, in small amounts, inhibits another microbe
- **Antimicrobial drugs:** synthetic substances that interfere with the growth of microbes

# The History of Chemotherapy (3 of 3)

- 1928: Fleming discovered penicillin, produced by **Penicillium**
- 1932: Prontosil red dye used for streptococcal infections
- 1940: First clinical trials of penicillin
- Today there is a growing problem of antibiotic resistance

# Figure 20.1 Laboratory Observation of Antibiosis

# Table 20.1 Representative Sources of Antibiotics (1 of 2)

**TABLE 20.1 Representative Sources of Antibiotics**

| Microorganism | Antibiotic |
|---|---|
| **Gram-Positive Rods** | |
| **Bacillus subtilis** | Bacitracin |
| **Paenibacillus polymyxa** | Polymyxin |
| **Actinomycetes** | |
| **Streptomyces nodosus** | Amphotericin B |
| **Streptomyces venezuelae** | Chloramphenicol |
| **Streptomyces aureofaciens** | Chlortetracycline and tetracycline |
| **Saccharopolyspora erythraea** | Erythromycin |
| **Streptomyces fradiae** | Neomycin |
| **Streptomyces griseus** | Streptomycin |
| **Micromonospora purpurea** | Gentamicin |

# Table 20.1 Representative Sources of Antibiotics (2 of 2)

| Microorganism | Antibiotic |
|---|---|
| **Fungi** | |
| **Cephalosporium** spp. | Cephalothin |
| **Penicillium griseofulvum** | Griseofulvin |
| **Penicillium chrysogenum** | Penicillin |

# Check Your Understanding-1

## Check Your Understanding

- ✓ Who coined the term **chemotherapy**?
  20-1
- ✓ More than half our antibiotics are produced by a certain genus of bacteria. What is it?
  20-2

# Spectrum of Antimicrobial Activity (1 of 2)

## Learning Objectives

20-3 Describe the problems of chemotherapy for viral, fungal, protozoan, and helminthic infections.

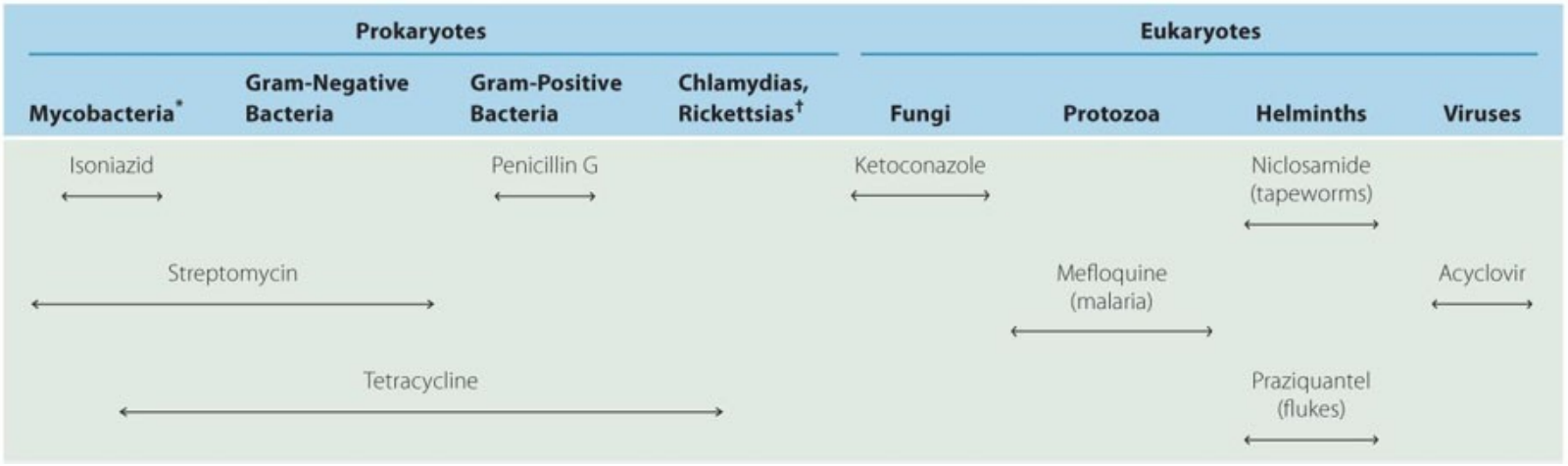
20-4 Define the following terms: **spectrum of activity, broad-spectrum antibiotic, superinfection**.

# Spectrum of Antimicrobial Activity (2 of 2)

- **Narrow spectrum of microbial activity:** drugs that affect a narrow range of microbial types
- **Broad-spectrum antibiotics:** affect a broad range of gram-positive or gram-negative bacteria
- **Superinfection:** overgrowth of normal microbiota that is resistant to antibiotics

# Table 20.2 The Spectrum of Activity of Antibiotics and Other Antimicrobial Drugs

## Table 20.2 The Spectrum of Activity of Antibiotics and Other Antimicrobial Drugs




*Growth of these bacteria frequently occurs within macrophages or tissue structures.

†Obligately intracellular bacteria.

# Check Your Understanding-2

## Check Your Understanding

- ✓ Identify at least one reason why it's so difficult to target a pathogenic virus without damaging the host's cells.
  20-3
- ✓ Why are antibiotics with a very broad spectrum of activity not as useful as one might first think?
  20-4

# The Action of Antimicrobial Drugs (1 of 6)

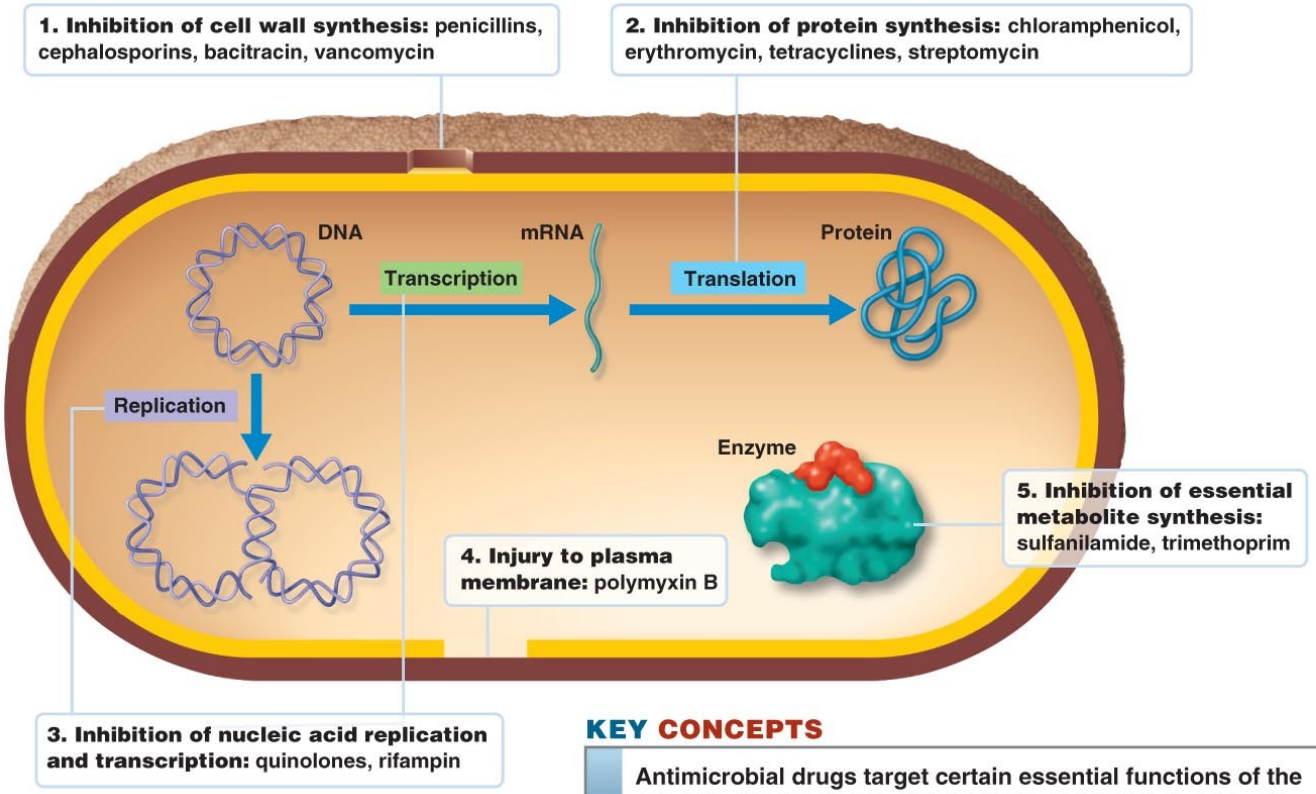
## Learning Objective

20-5 Identify five modes of action of antimicrobial drugs.

# The Action of Antimicrobial Drugs (2 of 6)

- **Bactericidal**
  - Kill microbes directly
- **Bacteriostatic**
  - Prevent microbes from growing

# Figure 20.2 Major Action Modes of Antibacterial Drugs




**KEY CONCEPTS**

Antimicrobial drugs target certain essential functions of the microbe. Mechanisms of action include inhibiting cell wall synthesis, inhibiting protein synthesis, inhibiting nucleic acid synthesis, injuring the plasma membrane, or inhibiting synthesis of essential metabolites.

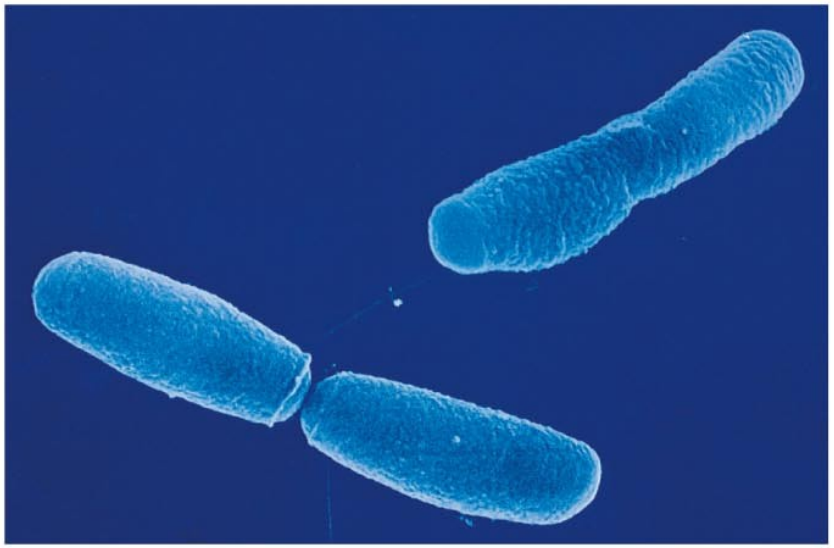
The antimicrobial drug must not interfere with essential functions of the microbe's host.

Pearson

# The Action of Antimicrobial Drugs (3 of 6)

- Inhibiting cell wall synthesis
  - Penicillins prevent the synthesis of peptidoglycan

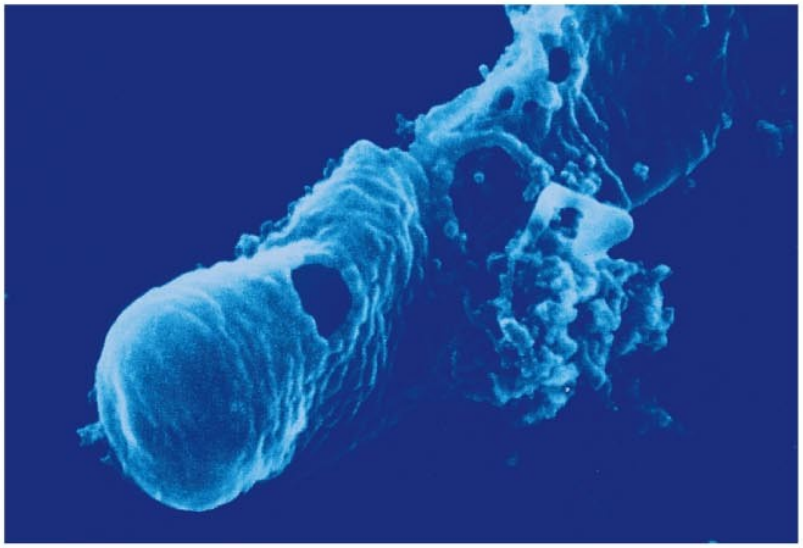
# Figure 20.3 The inhibition of bacterial cell wall synthesis by penicillin



**(a)** Rod-shaped bacterium before penicillin

SEM

1 $\mu$m



**(b)** The bacterial cell lysing as penicillin weakens the cell wall

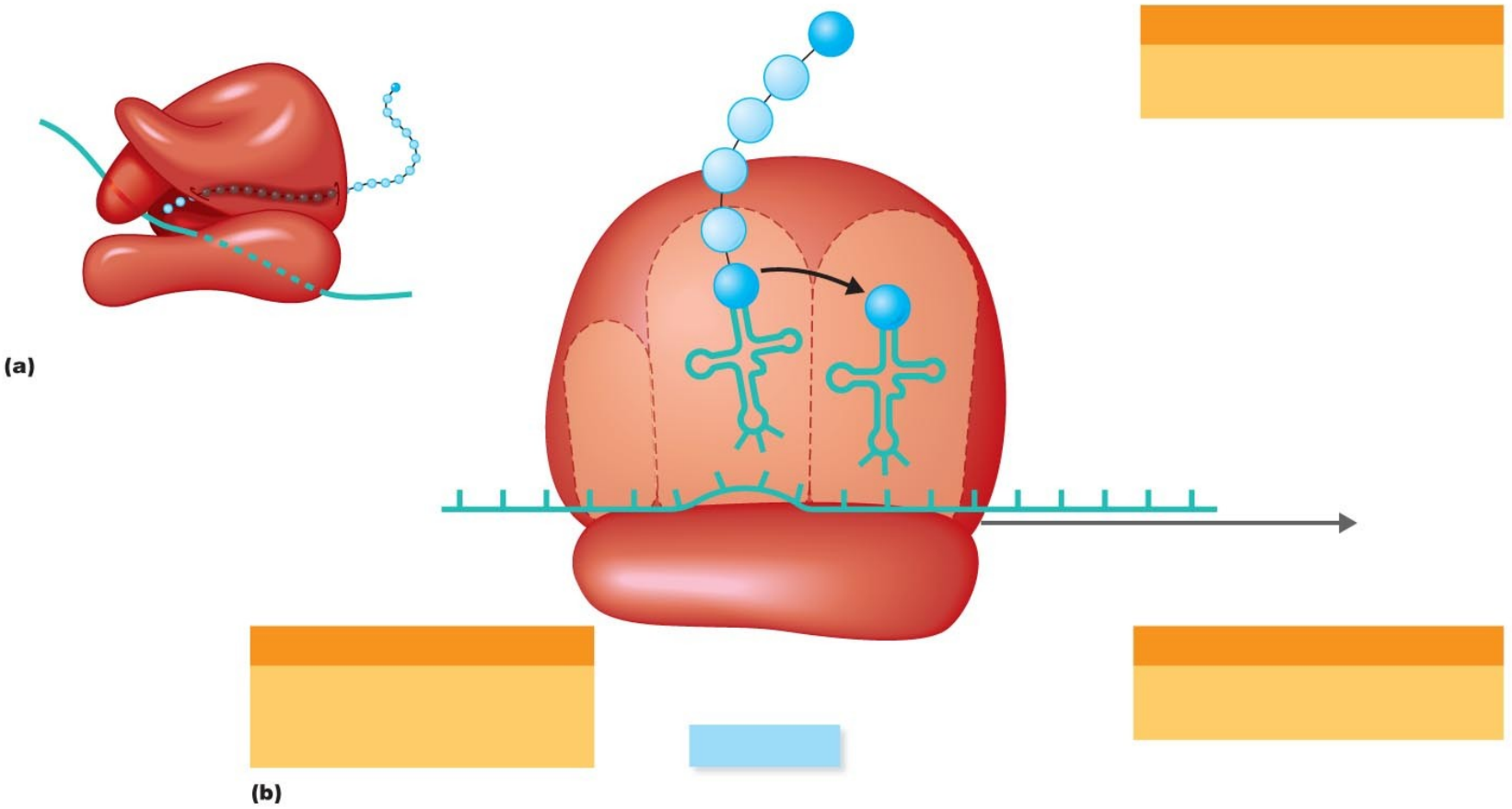
SEM

1 $\mu$m

# The Action of Antimicrobial Drugs (4 of 6)

- Inhibiting protein synthesis
  - Target bacterial 70S ribosomes
  - Chloramphenicol, erythromycin, streptomycin, tetracyclines

# Figure 20.4 The Inhibition of Protein Synthesis by Antibiotics



# The Action of Antimicrobial Drugs (5 of 6)

- Injuring the plasma membrane
  - Polypeptide antibiotics change membrane permeability
  - Antifungal drugs combine with membrane sterols

# Figure 20.5 Injury to the Plasma Membrane of a Yeast Cell Caused by an Antifungal Drug

# The Action of Antimicrobial Drugs (6 of 6)

- Inhibiting nucleic acid synthesis
  - Interfere with DNA replication and transcription
- Inhibiting the synthesis of essential metabolites
  - Antimetabolites compete with normal substrates for an enzyme
    - Sulfanilamide competes with **para-aminobenzoic acid (PABA),** stopping the synthesis of folic acid

# Check Your Understanding-3

## Check Your Understanding

- ✓ What cellular function is inhibited by tetracyclines?

  20-5

# Chemotherapeutic Agents: Modes of Action


**Animation: Chemotherapeutic Agents: Modes of Action**

# Common Antimicrobial Drugs (1 of 3)

## Learning Objectives

20-6 Explain why drugs in this section are bacteria-specific.

20-7 List the advantages of each of the following over penicillin: semisynthetic penicillins, cephalosporins, and vancomycin.

20-8 Explain why isoniazid and ethambutol are antimycobacterial agents.

# Common Antimicrobial Drugs (2 of 3)

## Learning Objectives

20-9 Describe how each of the following inhibits protein synthesis: aminoglycosides, tetracyclines, chloramphenicol, macrolides.

20-10 Compare polymyxin B, bacitracin, and neomycin in their modes of action.

20-11 Describe how rifamycins and quinolones kill bacteria.

20-12 Describe how sulfa drugs inhibit microbial growth.

# Common Antimicrobial Drugs (3 of 3)

## Learning Objectives

20-13 Explain modes of action of current antifungal drugs.

20-14 Explain modes of action of current antiviral drugs.

20-15 Explain modes of action of current antiprotozoan and antihelminthic drugs.

# Table 20.3 Antibacterial Drugs
(1 of 5)

| Drugs by Mode of Action | Comments |
|---|---|
| **Inhibitors of Cell Wall Synthesis** | |
| Natural Penicillins | |
| Penicillin G | Against gram-positive bacteria, requires injection |
| Penicillin V | Against gram-positive bacteria, oral administration |
| Semisynthetic Penicillins | |
| Oxacillin | Resistant to penicillinase |
| Ampicillin | Broad spectrum |
| Amoxicillin | Broad spectrum; combined with inhibitor of penicillinase |
| Aztreonam | A monobactam; effective against gram-negative bacteria, including **Pseudomonas** spp. |
| Imipenem | A carbapenem; very broad spectrum |
| Cephalosporins | |
| Cephalothin | First-generation cephalosporin; activity similar to penicillin; requires injection |
| Cefixime | Fourth-generation cephalosporin; oral administration |

# Table 20.3 Antibacterial Drugs
(2 of 5)

| Drugs by Mode of Action | Comments |
|---|---|
| **Inhibitors of Cell Wall Synthesis** | |
| Polypeptide Antibiotics | |
| Bacitracin | Against gram-positive bacteria; topical application |
| Vancomycin | A glycopeptide type; penicillinase-resistant; against gram-positive bacteria |
| Antimycobacterial Antibiotics | |
| Isoniazid | Inhibits synthesis of mycolic acid component of cell wall of **Mycobacterium** spp. |
| Ethambutol | Inhibits incorporation of mycolic acid into cell wall of **Mycobacterium** spp. |

# Table 20.3 Antibacterial Drugs
(3 of 5)

| Drugs by Mode of Action | Comments |
|---|---|
| **Inhibitors of Protein Synthesis** | |
| Chloramphenicol | Broad spectrum, potentially toxic |
| Aminoglycosides | |
| Streptomycin | Broad spectrum, including mycobacteria |
| Neomycin | Topical use, broad spectrum |
| Gentamicin | Broad spectrum, including *Pseudomonas* spp. |
| Pleuromutilins | |
| Mutilin, retpamulin | Inhibit gram-positive bacteria |
| Tetracyclines | |
| Tetracycline, oxytetracycline, chlortetracycline | Broad spectrum, including chlamydias and rickettsias; animal feed additives |

# Table 20.3 Antibacterial Drugs (4 of 5)

| Drugs by Mode of Action | Comments |
|---|---|
| **Inhibitors of Protein Synthesis** | |
| Macrolides | Alternative to penicillin |
| Erythromycin | Semisynthetic; broader spectrum and better tissue penetration than erythromycin |
| Azithromycin, clarithromycin | New generation of semisynthetic macrolides; used to cope with resistance to other macrolides |
| Telithromycin (Ketek) | |
| Streptogramins | |
| Quinupristin and dalfopristin (Synercid) | Alternative for treating vancomycin-resistant gram-positive bacteria |
| Oxazolidinones | |
| Linezolid (Zyvox) | Useful primarily against penicillin-resistant gram-positive bacteria |
| Glycylcyclines | |
| Tygecycline | Broad spectrum, especially MRSA and **Acinetobacter** |

# Table 20.3 Antibacterial Drugs (5 of 5)

| Drugs by Mode of Action | Comments |
|---|---|
| **Injury to the Plasma Membrane** | |
| Polymyxin B | Topical use, gram-negative bacteria, including **Pseudomonas** spp. |
| Lipopeptides | |
| Daptomycin | To treat MRSA infections |
| **Inhibitors of Nucleic Acid Synthesis** | |
| Rifamycins | |
| Rifampin | Inhibits synthesis of mRNA; treatment of tuberculosis |
| Quinolones and Fluoroquinolones | |
| Nalidixic acid, nofloxacin, ciprofloxacin | Inhibit DNA synthesis; broad spectrum; urinary tract infections |
| Gatifloxacin | Newest generation quinolone; increased potency against gram-positive bacteria |
| **Competitive Inhibitors of the Synthesis of Essential Metabolites** | |
| Sulfonamides | |
| Trimethoprim-sulfamethoxazole | Broad spectrum; combination is widely used |

# Table 20.4 Differential Grouping of Cephalosporins

## Table 20.4 Differential Grouping of Cephalosporins

| Generation | Description | Example |
|---|---|---|
| First | Relatively narrow level of activity, primarily against gram-negative bacteria | Cephalothin |
| Second | More extended gram-negative spectrum | Cefamdole (IV)<br>Cefaclor (oral) |
| Third | Most active against gram-negative bacteria, including some pseudomonads; must be injected | Ceftazidime |
| Fourth | Require injections; most extended spectrum of activity | Cefepime |

# Table 20.5 Antifungal, Antiviral, Antiprotozoan, and Antihelminthic Drugs (1 of 5)

**Table 20.5 Antifungal, Antiviral, Antiprotozoan, and**

| | Mode of Action | Comments |
|---|---|---|
| **Antifungal Drugs** | | |
| Agents Affecting Fungal Sterols (Plasma Membrane) | | |
| Polyenes | | |
| Amphotericin B | Injury to plasma membrane | Systemic fungal infections; fungicidal |
| Azoles | | |
| Clotrimazole, miconazole | Inhibit synthesis of plasma membrane | Topical use |
| Ketoconazole | Inhibits synthesis of plasma membrane | Can be taken orally for systemic fungal infections |
| Allylamines | | |
| Terbinafine, naftifine | Inhibit synthesis of plasma membrane | Treatment of diseases resistant to azoles |

# Table 20.5 Antifungal, Antiviral, Antiprotozoan, and Antihelminthic Drugs (2 of 5)

| | Mode of Action | Comments |
|---|---|---|
| Agents Affecting Fungal Cell Walls | | |
| Echinocandins | | |
| Caspofungin (Cancidas) | Inhibits synthesis of cell wall | Intravenous use only |
| Agents Inhibiting Nucleic Acids | | |
| Flucytosine | Inhibits RNA synthesis | Usually in combination with other antifungals |
| Other Antifungal Drugs | | |
| Griseofulvin | Inhibition of mitotic microtubules | Fungal infections of the skin |
| Tolnaftate | Unknown | Athlete’s foot |

# Table 20.5 Antifungal, Antiviral, Antiprotozoan, and Antihelminthic Drugs (3 of 5)

| | Mode of Action | Comments |
|---|---|---|
| Antiviral Drugs | | |
| Entry and Fusion Inhibitors | | |
| Maraviroc | Binds CCR5 | Treatment of HIV |
| Zanamivir, oseltamivir | Inhibit neuraminidase on influenza virus | Treatment of influenza |
| Uncoating Inhibitors | | |
| Amantadine, zimantadine | Inhibit uncoating | Treatment of influenza |
| Genome Integration and Nucleic Acid Synthesis Inhibitors | | |
| Zidovudine (AZT) | Inhibits DNA or RNA synthesis | Used primarily against HIV |
| Acyclovir, ganciclovir, ribavirin, lamivudine | Inhibit DNA or RNA synthesis | Used primarily against herpesviruses |
| Cidofovir | Inhibits DNA or RNA synthesis | Cytomegalovirus infections; possibly effective against smallpox |
| Adefovir dipivoxil (Hepsera) | Competitive inhibitor for HBV reverse transcriptase | Treatment of lamivudine-resistant infections |

# Table 20.5 Antifungal, Antiviral, Antiprotozoan, and Antihelminthic Drugs (4 of 5)

| | Mode of Action | Comments |
|---|---|---|
| Assembly and Exit Inhibitors | | |
| Saquinavir | Protease inhibitor | Treatment of HIV |
| Boceprevir | Protease inhibitor | Treatment of hepatitis C |
| Zanamivir, oseltamivir | Neuraminidase inhibitor | Treatment of influenza |
| Interferons | | |
| Alpha interferon | Inhibits spread of virus to new cells | Viral hepatitis |
| **Antiprotozoan Drugs** | | |
| Chloroquine | Inhibits DNA synthesis | Malaria; effective against red blood cell stage only |
| Diiodohydroxyquin | Unknown | Amebic infections; amebicidal |
| Metronidazole, tinidazole | Interfere with anaerobic metabolism | Giardiasis, amebiasis, trichomoniasis |

# Table 20.5 Antifungal, Antiviral, Antiprotozoan, and Antihelminthic Drugs (5 of 5)

| | Mode of Action | Comments |
|---|---|---|
| Antihelminthic Drugs | | |
| Niclosamide | Prevents ATP generation in mitochondria | Tapeworm infections; kills tapeworms |
| Praziquantel | Alters permeability of plasma membranes | Tapeworm and fluke infections; kills flatworms |
| Pyrantel pamoate | Neuromuscular block | Intestinal roundworms; kills roundworms |
| Mebendazole, albendazole | Inhibit absorption of nutrients | Intestinal roundworms |
| Ivermectin | Paralyzes worm | Intestinal roundworms primarily; occasional use for scabies mite and lice |

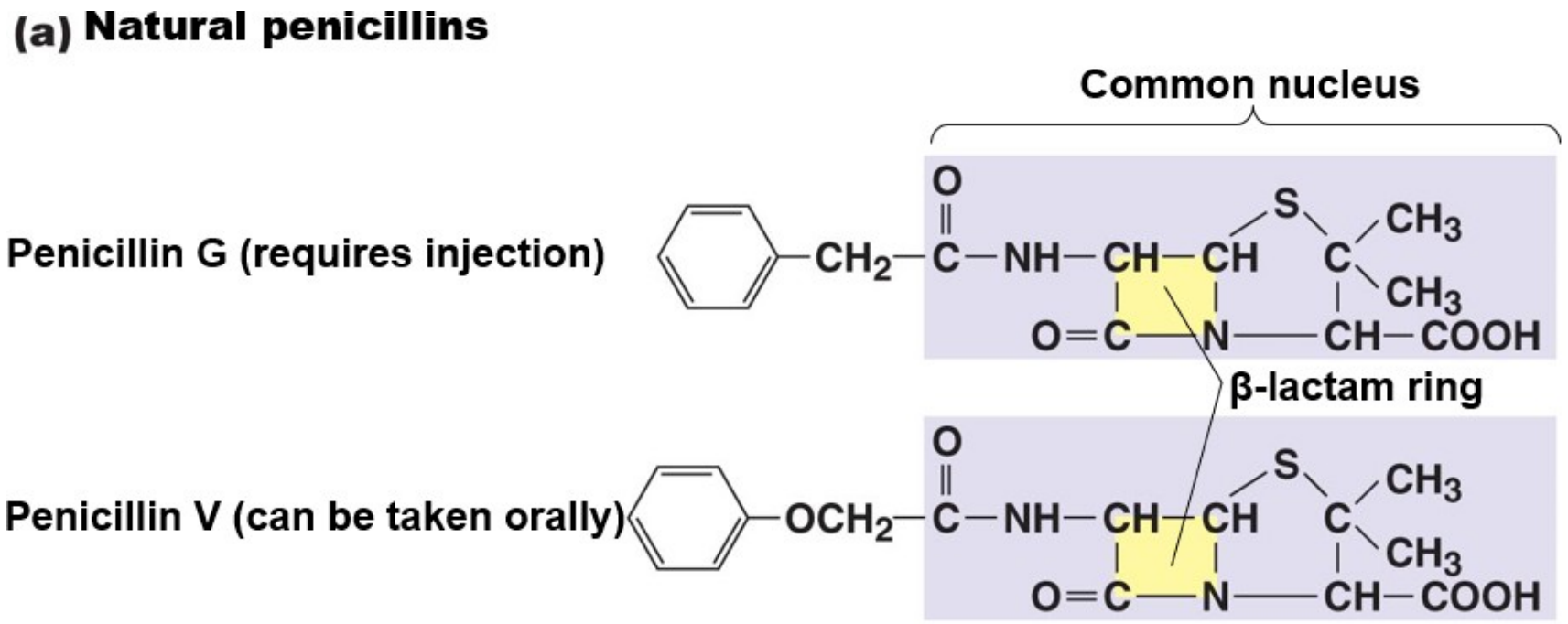
# Antibacterial Antibiotics: Inhibitors of Cell Wall Synthesis (1 of 2)

- **Penicillin**
  - Contain a $\beta$-lactam ring
    - Types are differentiated by the chemical side chains attached to the ring
  - Prevent the cross-linking of peptidoglycans, interfering with cell wall construction (especially gram-positives)

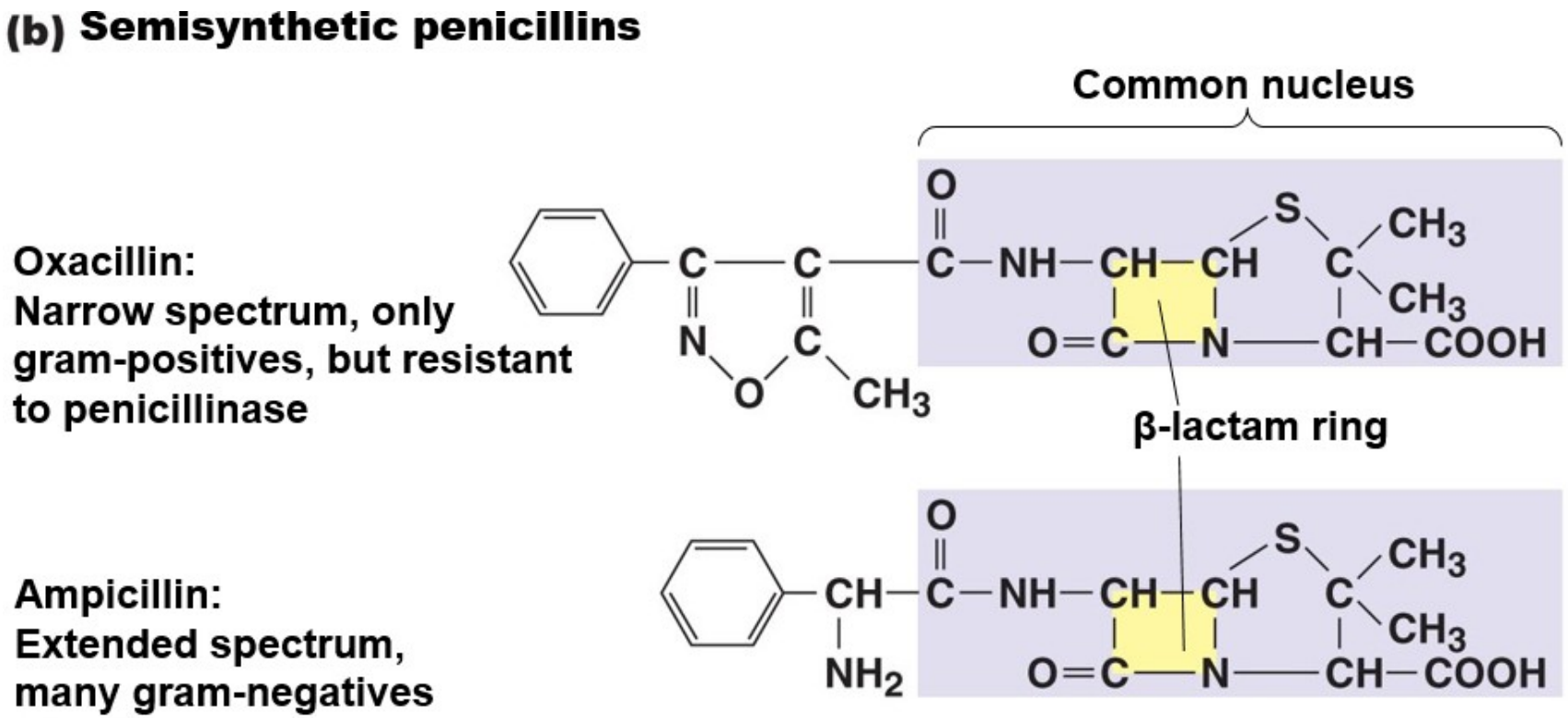
# Antibacterial Antibiotics: Inhibitors of Cell Wall Synthesis (2 of 2)

- **Natural penicillins**
  - Extracted from **Penicillium** cultures
    - Penicillin G (injected) and Penicillin V (oral)
  - Narrow spectrum of activity
  - Susceptible to penicillinases (β-lactamases)
- **Semisynthetic penicillins**
  - Contain chemically added side chains, making them resistant to penicillinases

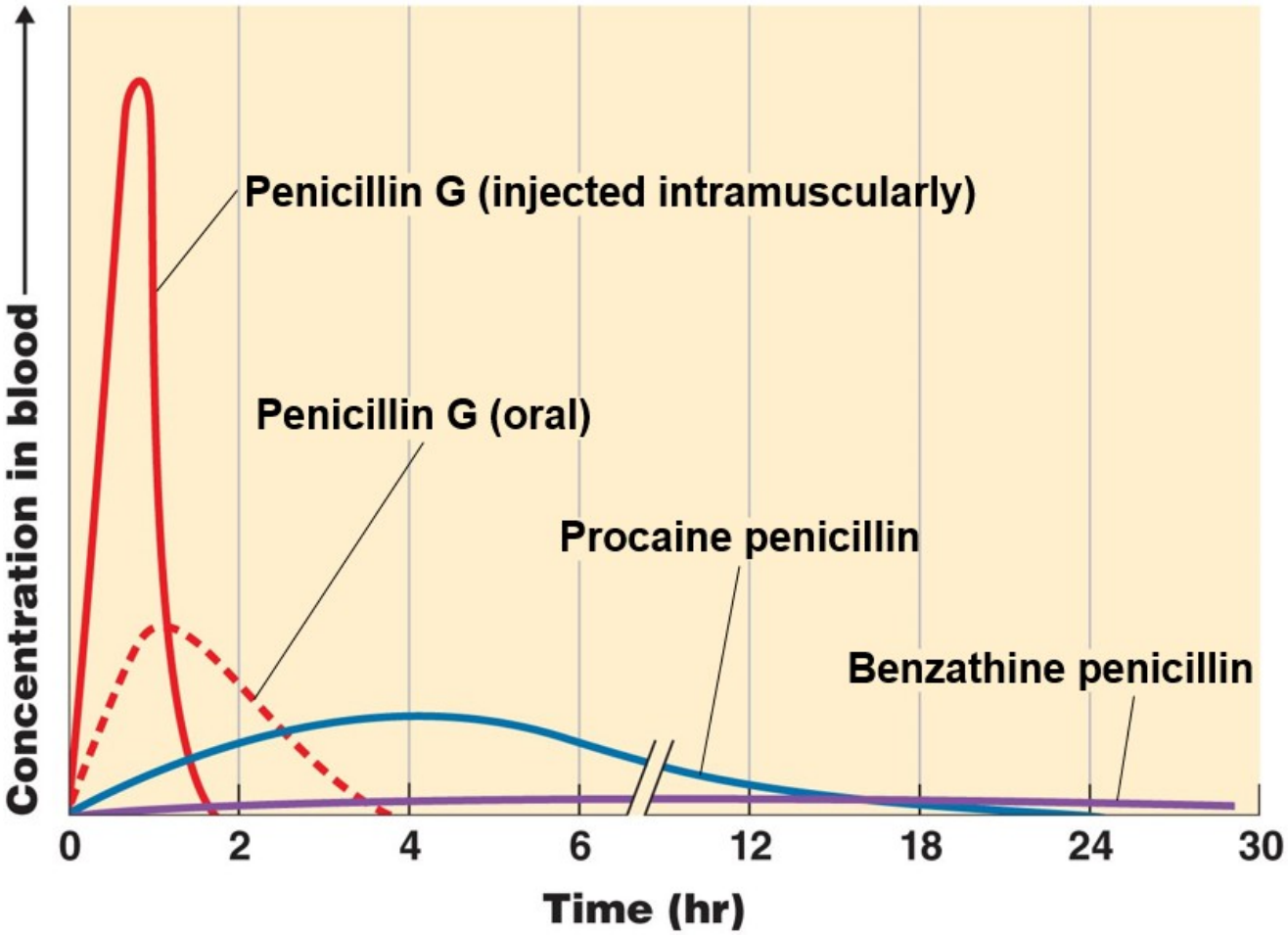
# Figure 20.6a The Structure of Penicillins, Antibacterial Antibiotics



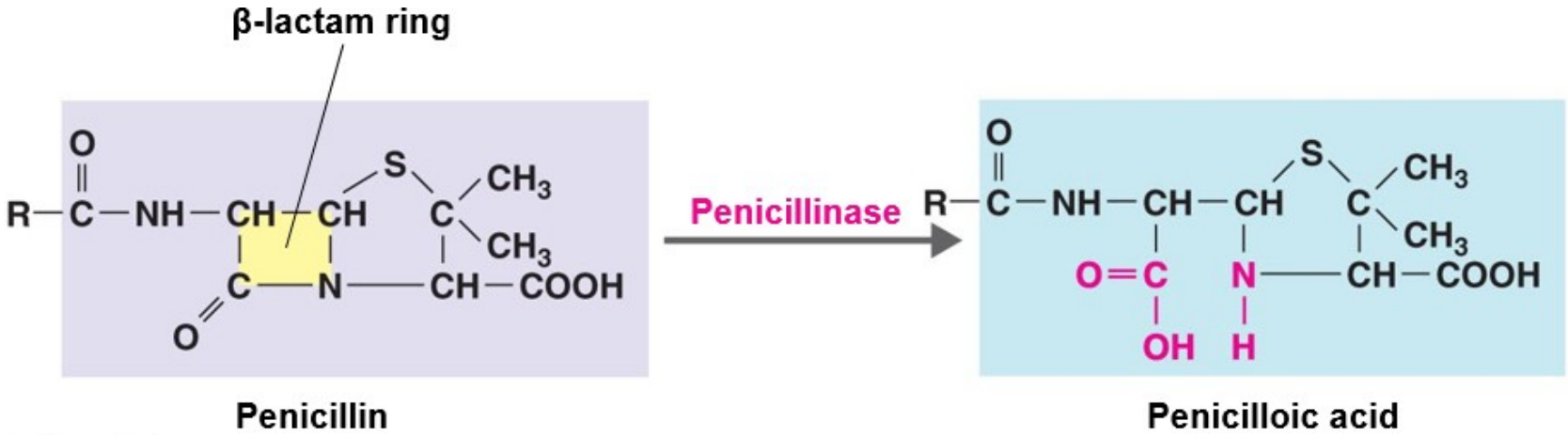
# Figure 20.6b The Structure of Penicillins, Antibacterial Antibiotics



# Figure 20.7 Retention of Penicillin G



# Figure 20.8 The Effect of Penicillinase on Penicillins



# Antibacterial Antibiotics: Inhibitors of Cell Wall Synthesis
(1 of 3)

- Penicillinase-resistant penicillins
  - Methicillin and oxacillin
- Extended-spectrum penicillins
  - Effective against gram-negatives as well as gram-positives
    - Aminopenicillins: ampicillin, amoxicillin
- Penicillins plus $\beta$-lactamase inhibitors
  - Contain clavulanic acid, a noncompetitive inhibitor of penicillinase

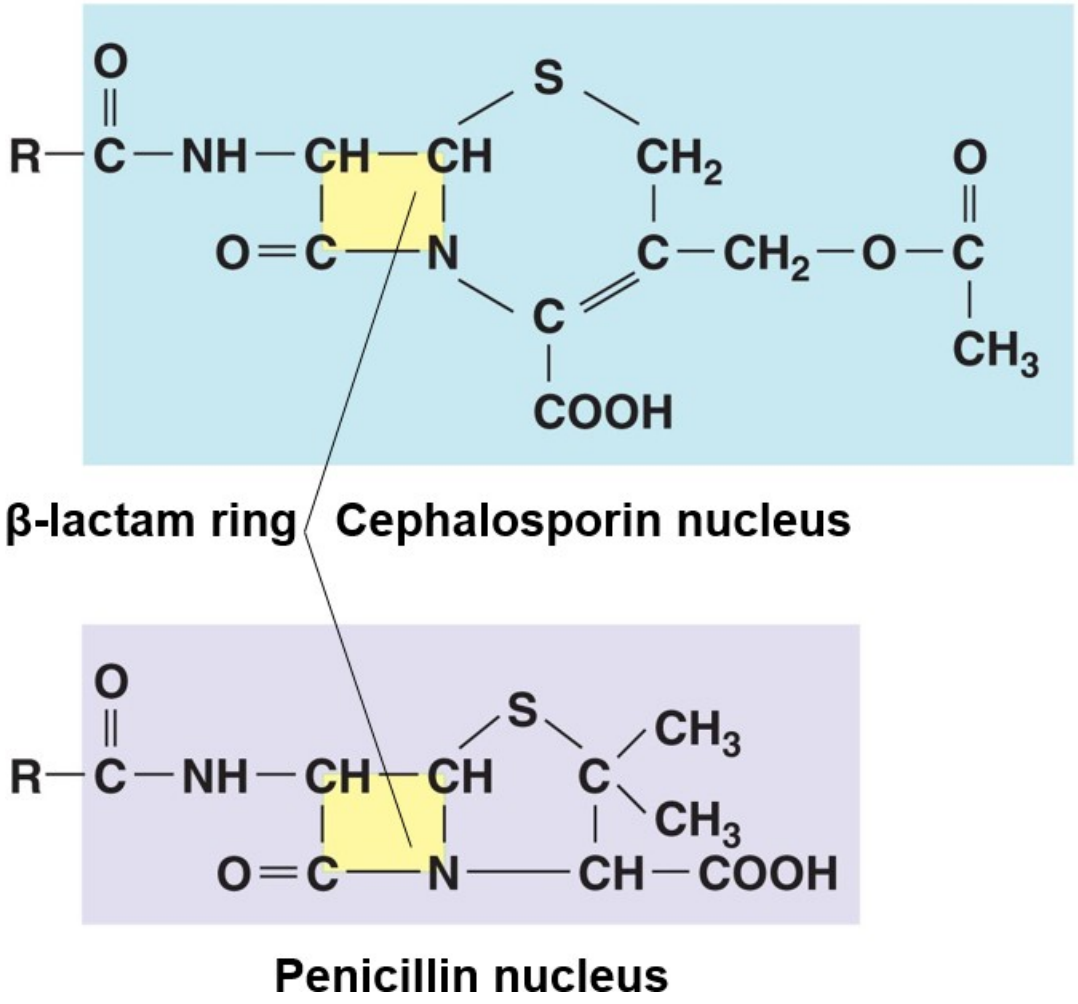
# Antibacterial Antibiotics: Inhibitors of Cell Wall Synthesis
(2 of 3)

- **Carbapenems**
  - Substitute a C for an S and add a double bond to the penicillin nucleus
  - Broad spectrum
    - Primaxin, doripenem
- **Monobactam**
  - Synthetic; single ring instead of the *β*-lactam double ring
  - Low toxicity; works against only certain gram-negatives
    - Aztreonam

# Antibacterial Antibiotics: Inhibitors of Cell Wall Synthesis
(3 of 3)

- **Cephalosporins**
  - Work similar to penicillins
  - β-lactam ring differs from penicillin
  - Grouped according to their generation of development
- Polypeptide antibiotics
  - Bacitracin
    - Topical application; works against gram-positives
  - Vancomycin
    - Glycopeptide
    - Last line against antibiotic-resistant MRSA

# Figure 20.9 The Nuclear Structures of Cephalosporin and Penicillin Compared



# Antimycobacterial Antibiotics

- **Isoniazid (INH)**
  - Inhibits the mycolic acid synthesis in mycobacteria
- **Ethambutol**
  - Inhibits incorporation of mycolic acid into the cell wall

# Check Your Understanding-4

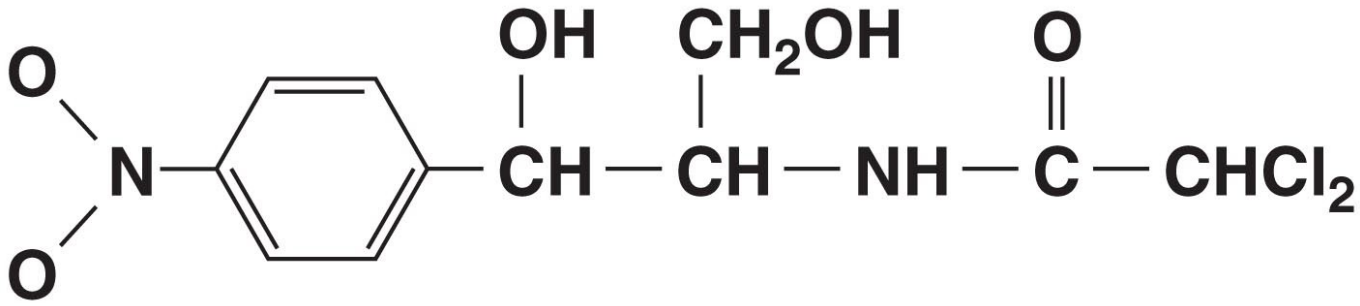
## Check Your Understanding

- ✓ One of the most successful groups of antibiotics targets the synthesis of bacterial cell walls; why does the antibiotic not affect the mammalian cell?
  20-6
- ✓ What phenomenon prompted the development of the first semisynthetic antibiotics, such as methicillin?
  20-7
- ✓ What genus of bacteria has mycolic acids in the cell wall?
  20-8

# Chloramphenicol

- Inhibits peptide bond formation
  - Binds to the 50S subunit of the 70S ribosome
- Synthesized chemically; broad spectrum
- Can suppress bone marrow and affect blood cell formation

# Figure 20.10 The Structure of the Antibacterial Antibiotic Chloramphenicol




Chloramphenicol

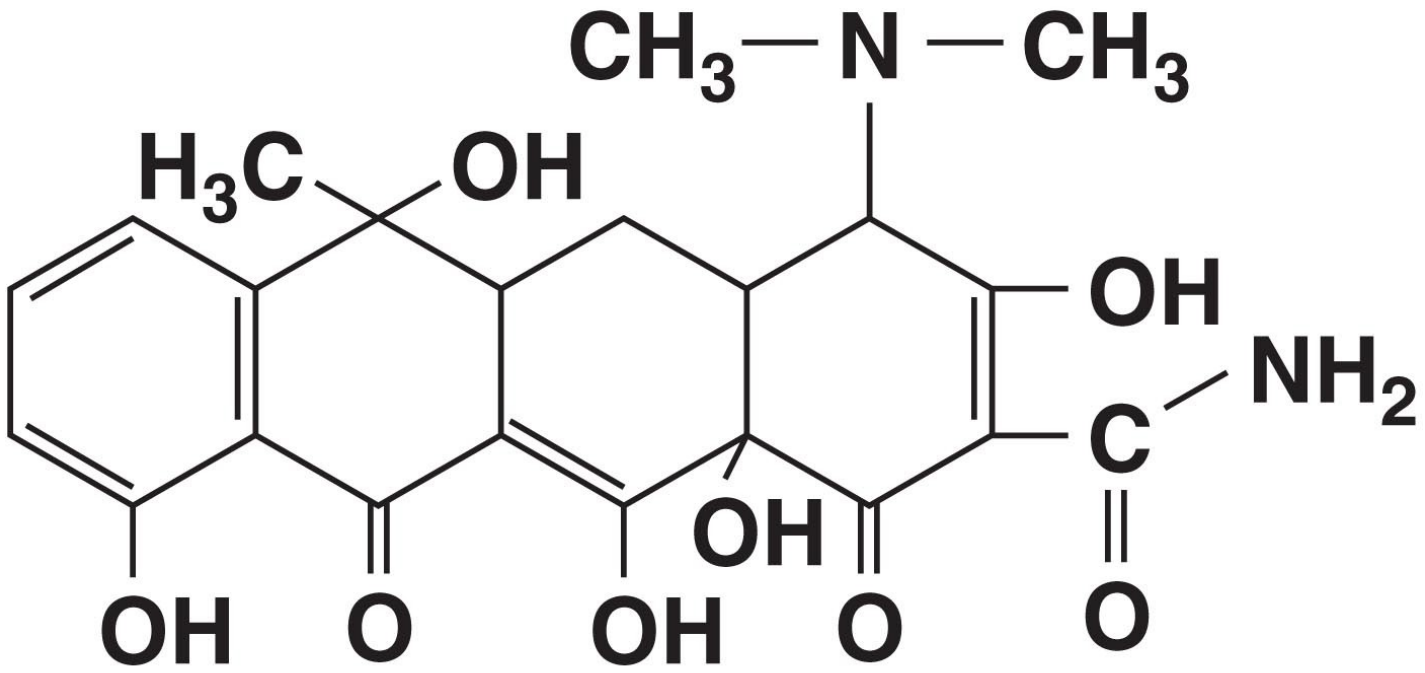
# Aminoglycosides

- Amino sugars linked by glycoside bonds
- Change the shape of the 30S subunit of the 70S ribosome
- Can cause auditory damage
- Streptomycin, neomycin, gentamicin

# Tetracyclines

- Produced by **Streptomyces** spp.
- Interfere with the tRNA attachment to the ribosome
- Broad spectrum; penetrate tissues, making them valuable against rickettsias and chlamydias
- Can suppress normal intestinal microbiota

# Figure 20.11 The Structure of the Antibacterial Antibiotic Tetracycline

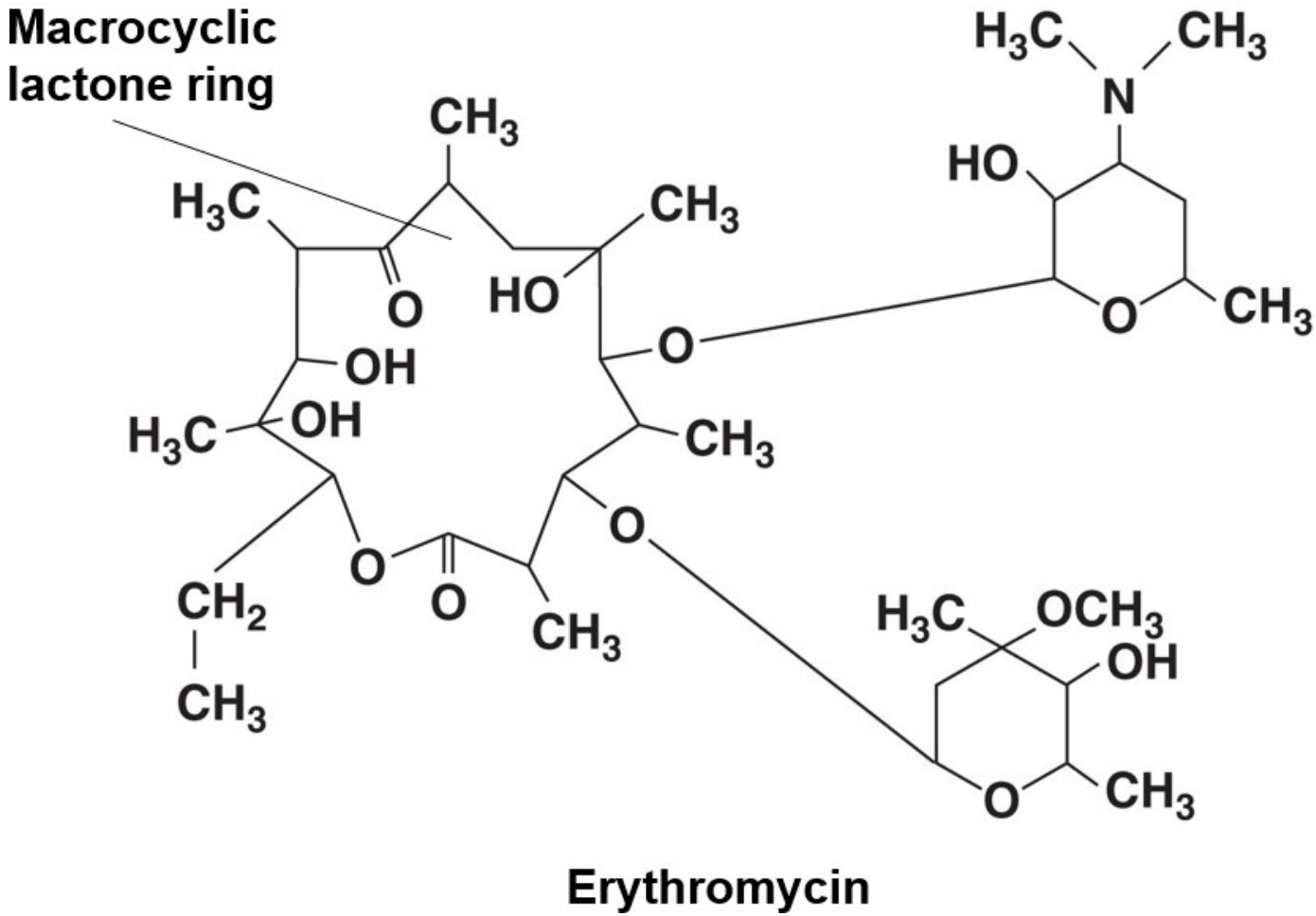



Tetracycline

# Inhibitors of Protein Synthesis
(1 of 2)

- **Glycylcyclines**
  - Broad spectrum; bacteriostatic
  - Bind to the 30S ribosomal subunit
  - Inhibits rapid efflux; administered intravenously
  - Useful against MRSA
- **Macrolides**
  - Contain a macrocyclic lactone ring
  - Narrow spectrum against gram-positives
    - Erythromycin

# Figure 20.12 The Structure of the Antibacterial Antibiotic Erythromycin, a Representative Macrolide




Erythromycin

# Inhibitors of Protein Synthesis
(2 of 2)

- **Streptogramins**
  - Attach to the 50S subunit
  - Work against gram-positives that are resistant to other antibiotics
- Oxazolidinones
  - Bind to the 50S/30S subunit interface
  - Synthetic; combat MRSA (linezolid)
- Pleuromutilins
  - Retapamulin: topical and effective against gram-positives

# Check Your Understanding-5

## Check Your Understanding

- ✓ Why does erythromycin, a macrolide antibiotic, have activity limited largely to gram-positive bacteria even though its mode of action is similar to that of the broad-spectrum tetracyclines?
  20-9

# Injury to the Plasma Membrane

- Affects synthesis of bacterial plasma membranes
- **Lipopeptide**
  - Daptomycin
    - Produced by streptomycetes; used for skin infections
    - Attacks the bacterial cell membrane
  - Polymyxin B
    - Topical; bacteriocidal; effective against gram-negatives
    - Combined with bacitracin and neomycin in nonprescription ointments

# Check Your Understanding-6

## Check Your Understanding

- ✓ Of the three drugs often found in over-the-counter antiseptic creams—polymyxin B, bacitracin, and neomycin—which has a mode of action most similar to that of penicillin? 20-10

# Nucleic Acid Synthesis Inhibitors

- **Rifamycin**
  - Inhibits mRNA synthesis
  - Penetrates tissues; antitubercular activity
- **Quinolone** and **fluoroquinolones**
  - Nalidixic acid
    - Synthetic; inhibits DNA gyrase
  - Norfloxacin and ciprofloxacin
    - Broad spectrum; relatively nontoxic

# Check Your Understanding-7

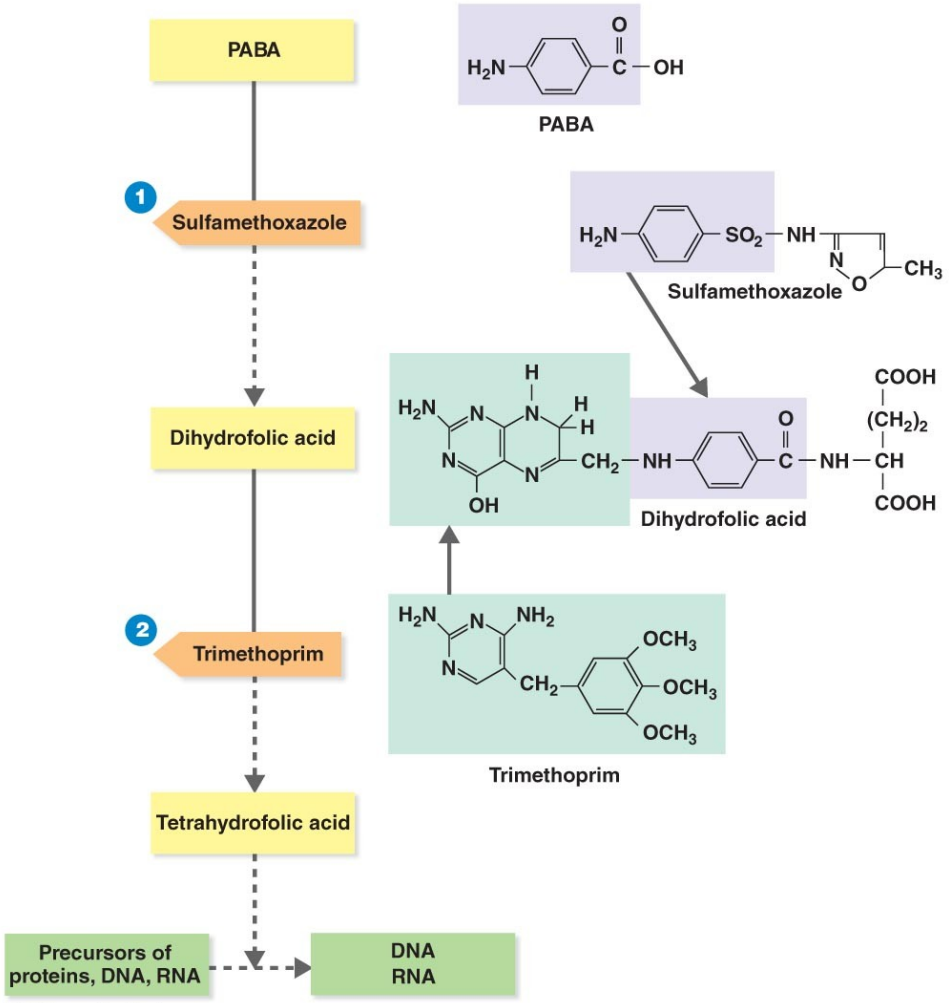
## Check Your Understanding

- ✓ What group of antibiotics interferes with the DNA-replicating enzyme DNA gyrase?
  20-11

# Sulfonamides

- Inhibit the folic acid synthesis needed for nucleic acid and protein synthesis
- Competitively bind to the enzyme for PABA production, a folic acid precursor
- Combination of trimethoprim and sulfamethoxazole (TMP-SMZ) is an example of drug **synergism**

# Figure 20.13 Actions of the Antibacterial Synthetics Trimethoprim and Sulfamethoxazole

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# Check Your Understanding-8

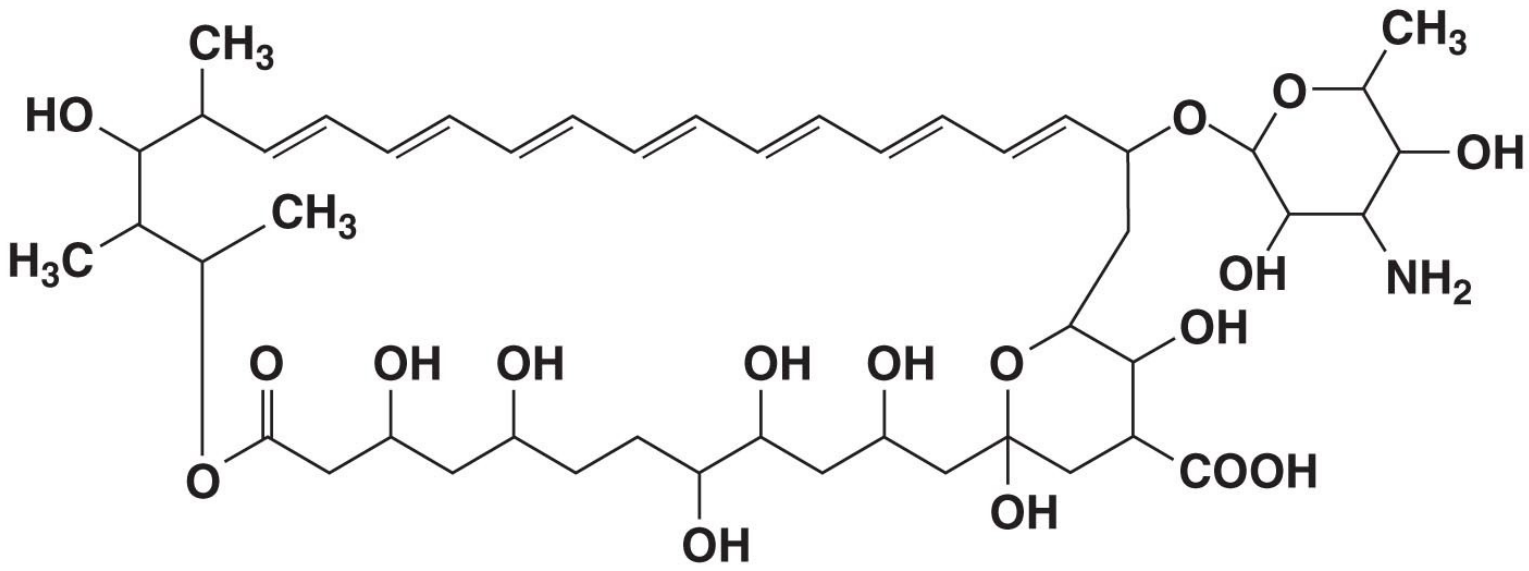
## Check Your Understanding

- ✓ Both humans and bacteria need PABA to make folic acid, so why do sulfa drugs adversly impact only bacterial cells?
  20-12

# Antifungal Drugs

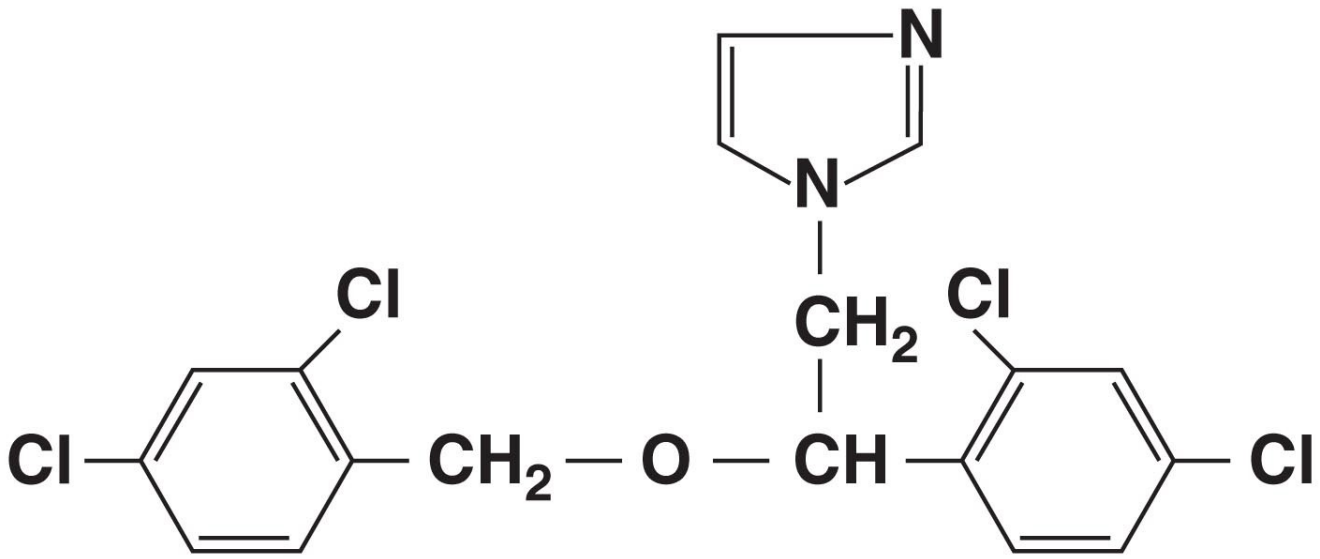
- Agents affecting fungal sterols
  - Interrupt the synthesis of ergosterol, making the membrane excessively permeable
  - Polyenes
    - Amphotericin B: produced by **Streptomyces;** toxic to the kidneys
  - Azoles
    - **Imidazoles:** topical; treat cutaneous mycoses
    - **Triazole:** treat systemic fungal infections
  - **Allylamines**
    - For azole-resistant infections

# Figure 20.14 The Structure of the Antifungal Drug Amphotericin B, Representative of the Polyenes




Amphotericin B

# Figure 20.15 The Structure of the Antifungal Drug Miconazole, Representative of the Imidazoles




Miconazole

# Antifungal Drugs (1 of 2)

- Agents affecting fungal cell walls
  - **Echinocandins**
    - Inhibit the synthesis of β-glucan
- Agents inhibiting nucleic acids
  - Flucytosine
    - Cytosine analog interferes with RNA synthesis

# Antifungal Drugs (2 of 2)

- Griseofulvin
  - Produced by **Penicillium**
  - Inhibits microtubule formation
  - Active against superficial dermatophytes
- Tolnaftate
  - For athlete's foot
- Pentamidine
  - Anti-**Pneumocystis**; may bind to DNA

# Check Your Understanding-9

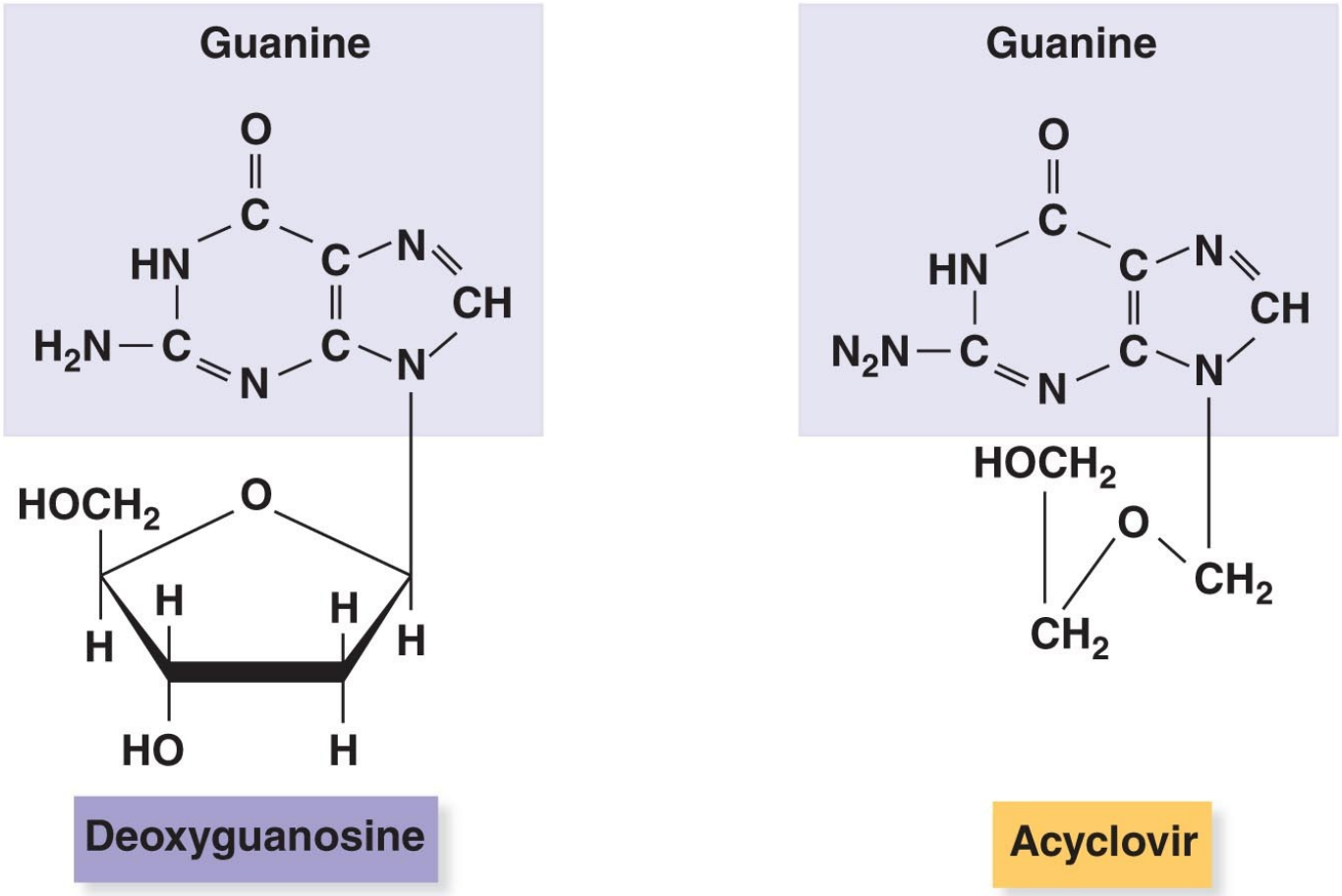
## Check Your Understanding

- ✓ What sterol in the cell membrane of fungi is the most common target for antifungal action?
  20-13

# Antiviral Drugs (1 of 2)

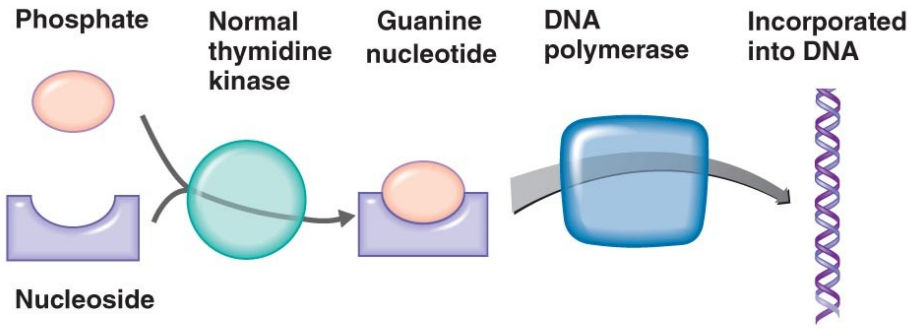
- Entry and fusion inhibitors
  - Block the receptors on the host cell that bind to the virus
  - Block fusion of the virus and cell
- Uncoating, genome integration, and nucleic acid synthesis inhibitors
  - Prevent viral uncoating
  - Inhibit viral DNA integration into the host genome
  - Nucleoside analogs inhibit RNA or DNA synthesis

# Figure 20.16a The Structure and Function of the Antiviral Drug Acyclovir

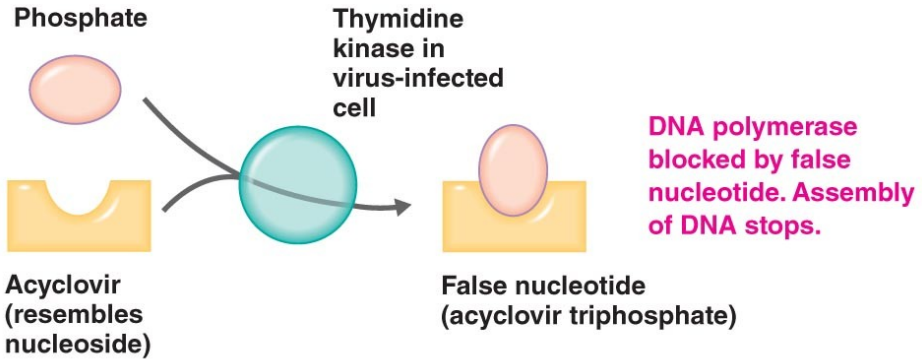



**(a) Acyclovir structurally resembles the nucleoside deoxyguanosine.**

# Figure 20.16b-C The Structure and Function of the Antiviral Drug Acyclovir




**(b)** The enzyme thymidine kinase combines phosphates with nucleosides to form nucleotides, which are then incorporated into DNA.




**(c)** Acyclovir has no effect on a cell not infected by a virus, that is, with normal thymidine kinase. In a virally infected cell, the thymidine kinase is altered and converts the acyclovir (which resembles the nucleoside deoxyguanosine) to a false nucleotide, which blocks DNA synthesis by DNA polymerase.

# Antiviral Drugs (2 of 2)

- Interference with assembly and release of viral particles
  - **Protease inhibitors**
    - Block the cleavage of protein precursors
- Exit inhibitors
  - Inhibit neuraminidase, an enzyme required for some viruses to bud from the host cell

# Interferons

- Produced by viral-infected cells to inhibit further spread of the infection
- Imiquimod
  - Promotes interferon production

# Check Your Understanding-10

## Check Your Understanding

- ✓ One of the most widely used antivirals, acyclovir, inhibits the synthesis of DNA. Humans also synthesize DNA, so why is the drug still useful in treating viral infections?
  20-14

# Antivirals for Treating HIV/AIDS

- **Antiretroviral**
  - **Nucleoside analog** (zidovudine)
  - **Nucleotide analog** (tenofovir)
  - **Non-nucleoside inhibitors** (nevirapine)
  - Protease inhibitors (atazanavir)
  - Integrase inhibitors (raltegravir)
  - Entry inhibitors (miraviroc)
  - Fusion inhibitors (enfuvirtide)

# Antiprotozoan and Antihelminthic Drugs (1 of 2)

- Antiprotozoan drugs
  - Quinine and chloroquine
    - Treat malaria
  - Artemisinin
    - Kills **Plasmodium** that causes malaria
  - Metronidazole (Flagyl)
    - Also interferes with anaerobic bacteria
    - Treats **Trichomonas,** giardiasis, and amebic dysentery

# Antiprotozoan and Antihelminthic Drugs (2 of 2)

- Antihelminthic drugs
  - Niclosamide
    - Prevents ATP production
      - Treats tapeworms
  - Praziquantel
    - Alters membrane permeability
      - Treats tapeworms and flukes
  - Mebendazole and albendazole
    - Interfere with nutrient absorption
      - Treat intestinal helminths
  - Ivermectin
    - Paralysis of helminths
      - Treats roundworms and mites

# Check Your Understanding-11

## Check Your Understanding

- ✓ What was the first drug for parasitic infections? 20-15

# Tests to Guide Chemotherapy

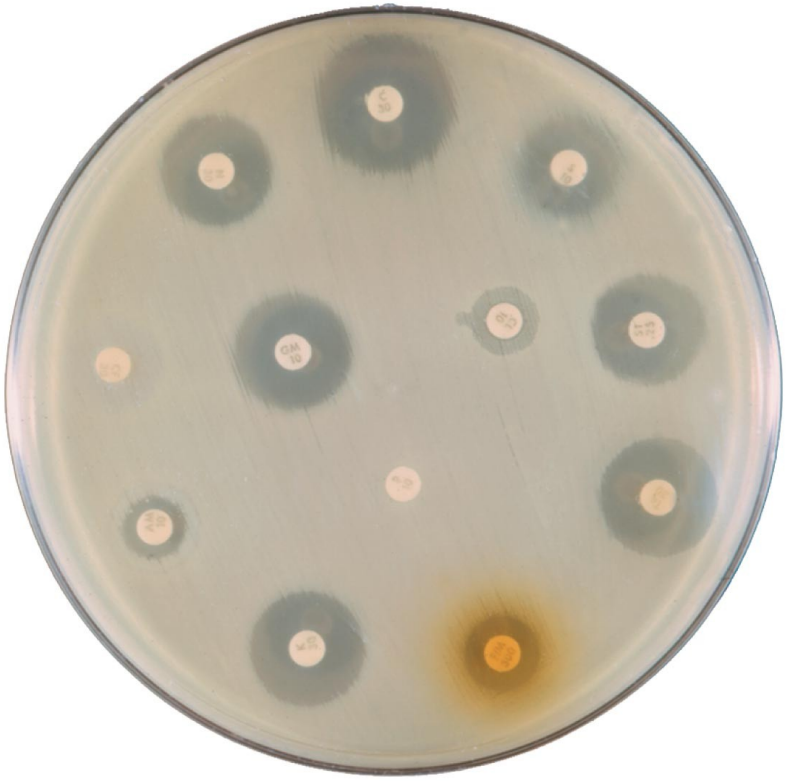
## Learning Objective

20-16 Describe two tests for microbial susceptibility to chemotherapeutic agents.

# The Diffusion Methods (1 of 2)

- **Disk-diffusion method** (Kirby-Bauer test)
  - Tests the effectiveness of chemotherapeutic agents
    - Paper disks with a chemotherapeutic agent are placed on agar containing the test organism
    - **Zone of inhibition** around the disk determines the sensitivity of the organism to the antibiotic

# Figure 20.17 The Disk-Diffusion Method for Determining the Activity of Antimicrobials

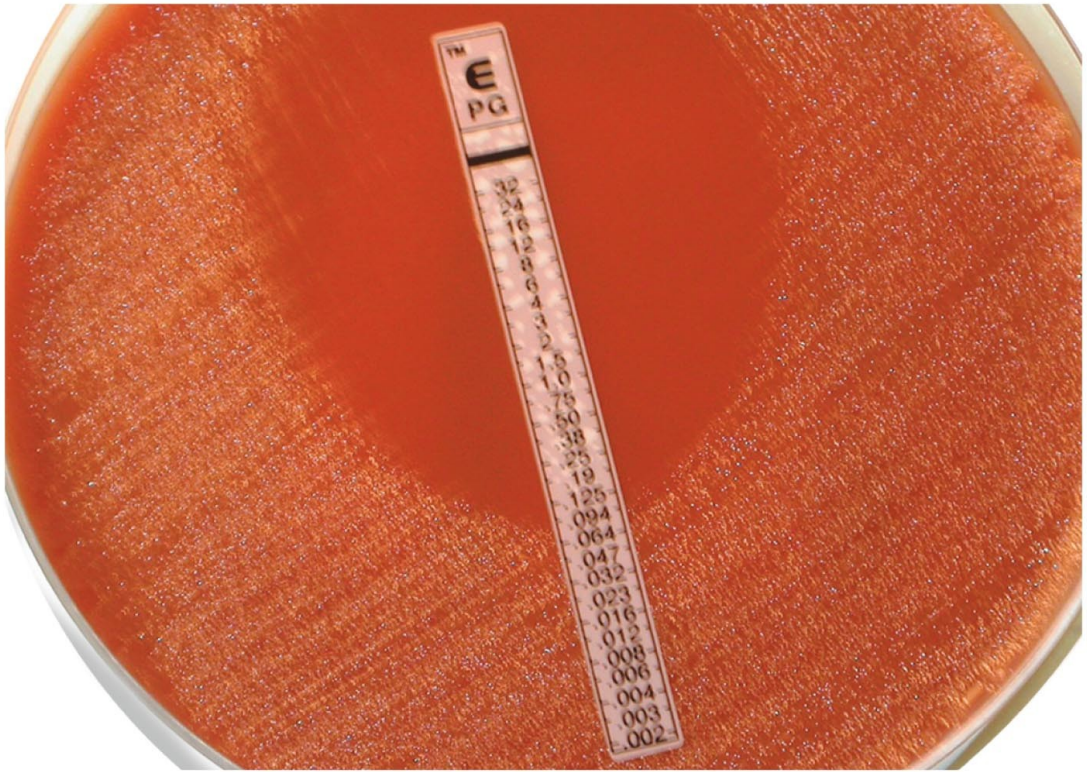


# The Diffusion Methods (2 of 2)

- **E test**
  - Determines the **minimal inhibitory concentration (MIC)**
    - Lowest antibiotic concentration preventing bacterial growth

# Figure 20.18 the E Test (for Epsilometer)

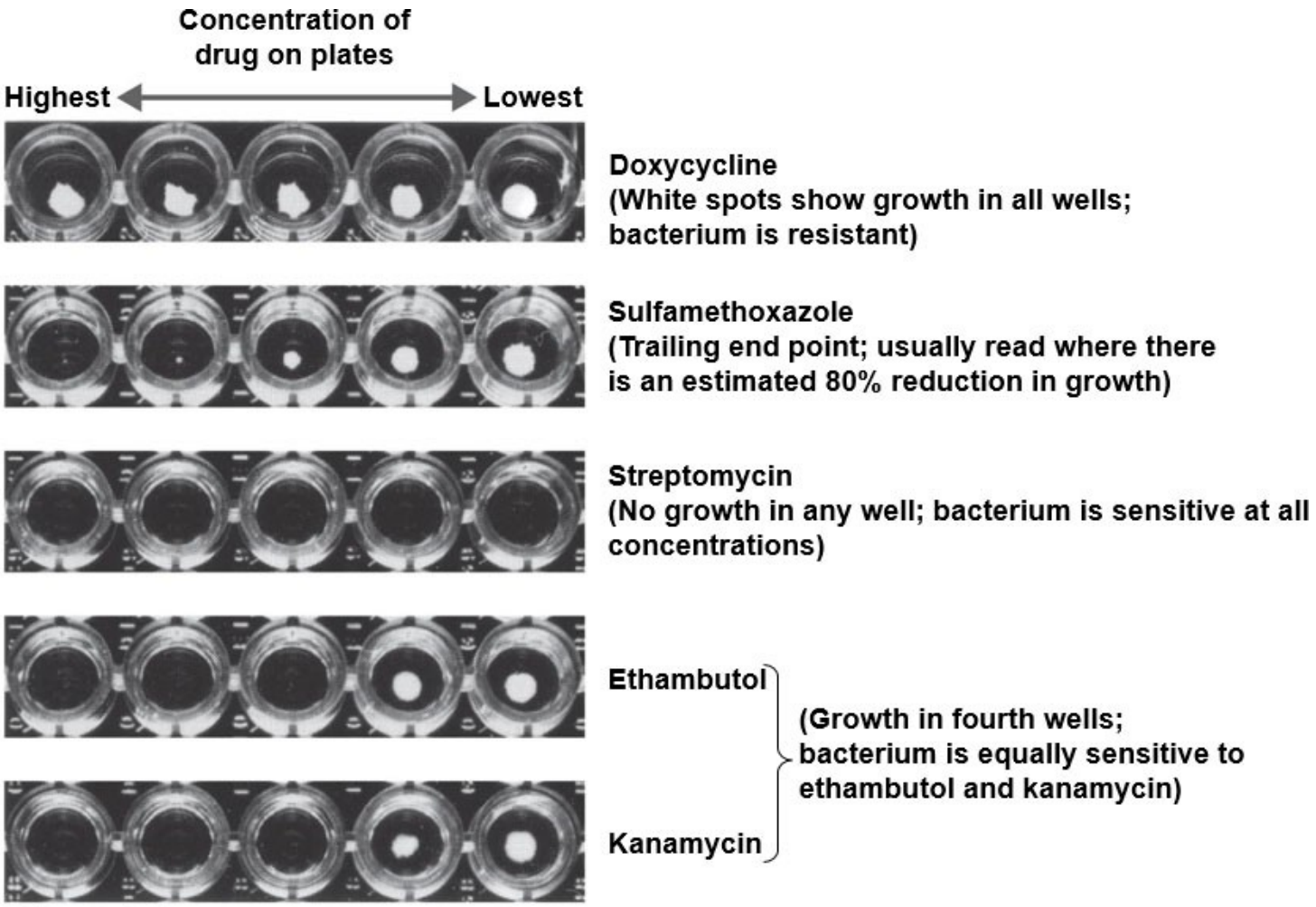
The E test (for epsilometer), a gradient diffusion method that determines antibiotic sensitivity and estimates minimal inhibitory concentration (MIC).



# Broth Dilution Tests

- Determine the MIC and **minimal bactericidal concentration (MBC)** of an antimicrobial drug
- Test organism is placed into the wells of a tray containing dilutions of a drug; growth is determined
- **Antibiograms**
  - Reports that record the susceptibility of organisms encountered clinically

# Microtiter, Plate Used for Testing for Minimal Inhibitory Concentration (MIC) of Antibiotics



# Check Your Understanding-12

## Check Your Understanding

- ✓ In the disk-diffusion test, the zone of inhibition indicating sensitivity around the disk varies with the antibiotic. Why?
  20-16

# Resistance to Antimicrobial Drugs (1 of 2)

## Learning Objective

20-17 Describe the mechanisms of drug resistance.

# Resistance to Antimicrobial Drugs (2 of 2)

- **Persister cells:** microbes with genetic characteristics allowing for their survival when exposed to an antibiotic
- **Superbugs:** bacteria that are resistant to large numbers of antibiotics
- Resistance genes are often spread horizontally among bacteria on plasmids or transposons via conjugation or transduction

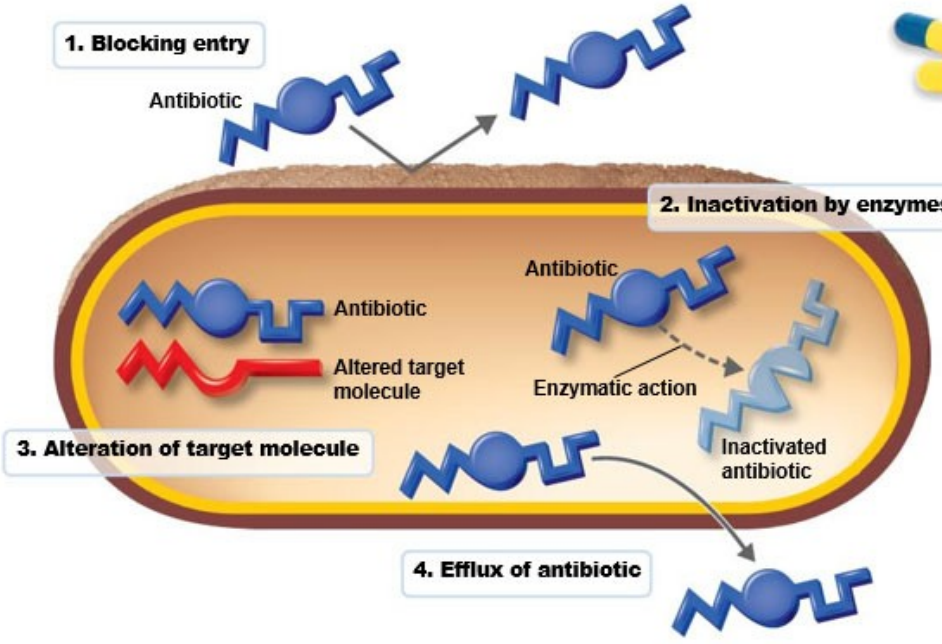
# Antibiotic Resistance: Origins of Resistance

PLAY **Animation: Antibiotic Resistance: Origins of Resistance**

# Mechanisms of Resistance

- Enzymatic destruction or inactivation of the drug
- Prevention of penetration to the target site within the microbe
- Alteration of the drug's target site
- Rapid efflux (ejection) of the antibiotic
- Variations of mechanisms of resistance

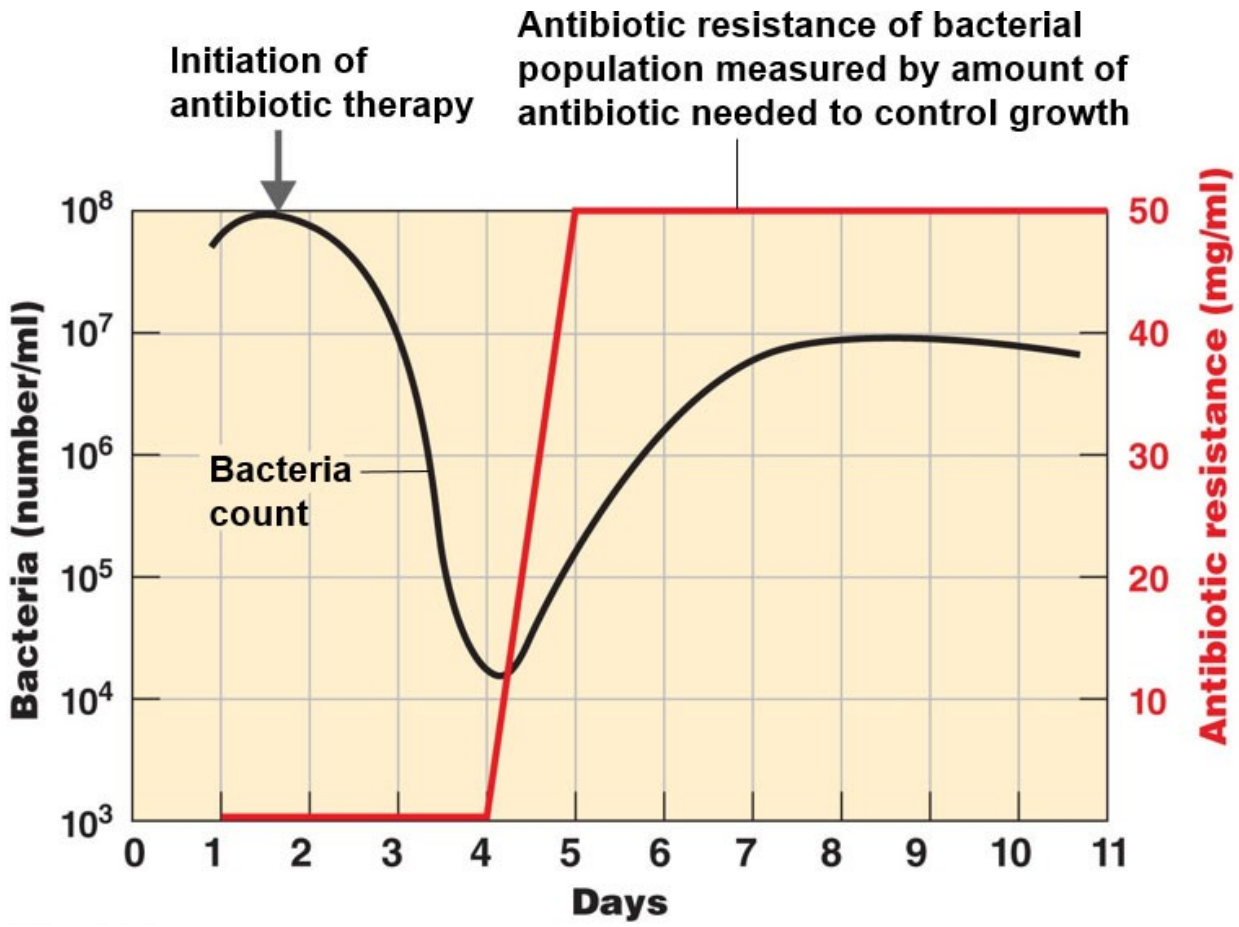
# Figure 20.20 Bacterial Resistance to Antibiotics




**KEY CONCEPTS**

- There are only a few mechanisms of microbial resistance to antimicrobial agents: blocking the drug's entry into the cell, inactivation of the drug by enzymes, alteration of the drug's target site, efflux of the drug from the cell, or alteration of the metabolic pathways of the host.
- The mechanisms of bacterial resistance to antibiotics are limited. Knowledge of these mechanisms is critical for understanding the limitations of antibiotic use.

# Figure 20.21 The Development of an Antibiotic-Resistant Mutant During Antibiotic Therapy



# Antibiotic Resistance: Forms of Resistance

PLAY **Animation: Antibiotic Resistance: Forms of Resistance**

# Antibiotic Misuse

- Misuse of antibiotics selected for resistance mutants
- Misuse includes:
  - Using outdated or weakened antibiotics
  - Using antibiotics for the common cold and other inappropriate conditions
  - Using antibiotics in animal feed
  - Failing to complete the prescribed regimen
  - Using someone else's leftover prescription

# Check Your Understanding-13

## Check Your Understanding

- ✓ What is the most common mechanism that a bacterium uses to resist the effects of penicillin?

  20-17

# Antibiotic Safety

- Therapeutic index: risk versus benefit
- Reactions of antibiotics with other drugs
- Damage to organs
- Risk to the fetus

# Effects of Combinations of Drugs (1 of 2)

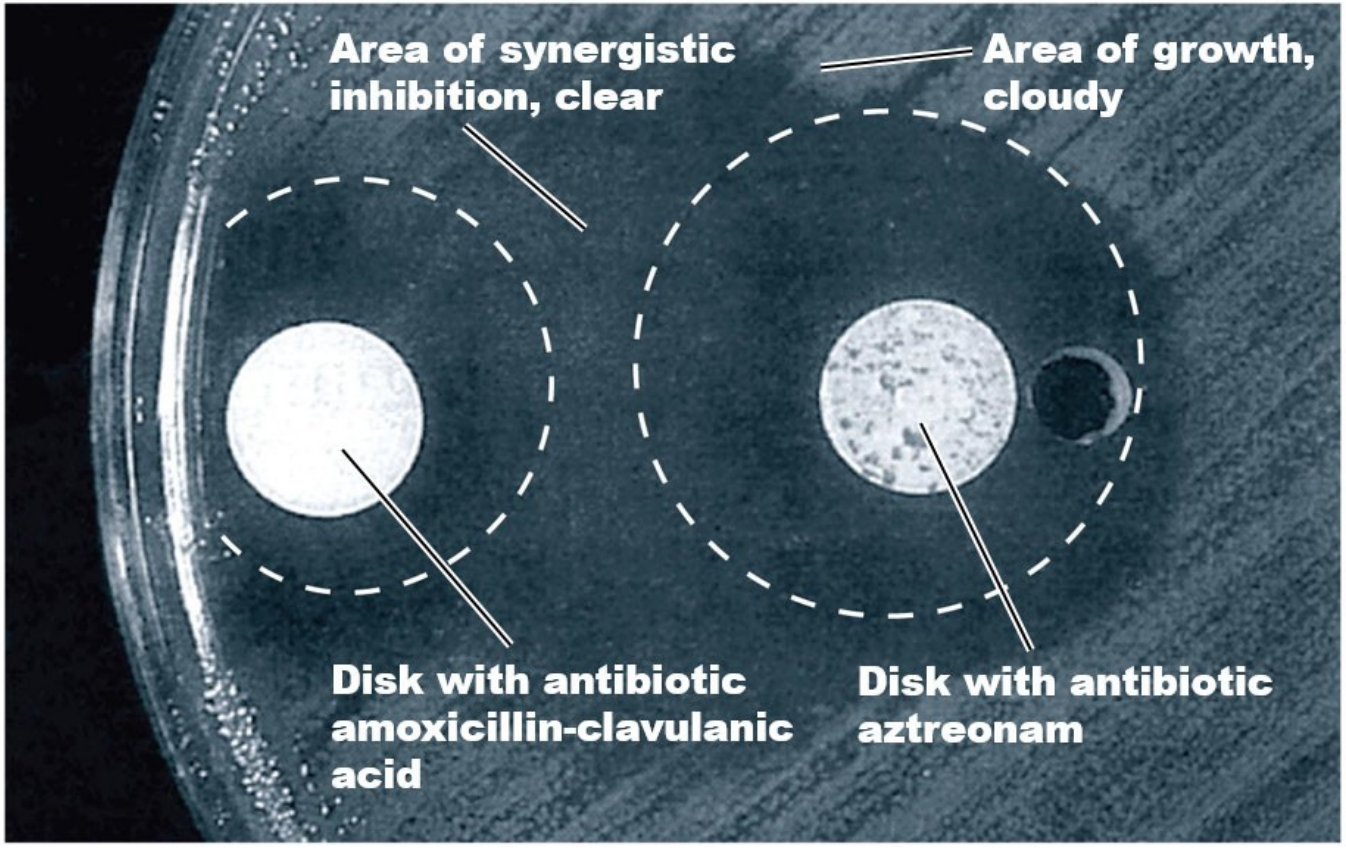
## Learning Objective

20-18 Compare and contrast synergism and antagonism.

# Effects of Combinations of Drugs (2 of 2)

- **Synergism:** the effect of two drugs together is greater than the effect of either alone
- **Antagonism:** the effect of two drugs together is less than the effect of either alone

# Figure 20.23 An Example of Synergism Between Two Different Antibiotics




Pearson

# Check Your Understanding-14

## Check Your Understanding

- ✓ Tetracycline sometimes interferes with the activity of penicillin. How?
  20-18

# Future of Chemotherapeutic Agents (1 of 2)

## Learning Objective

20-19 Name three areas of research on new chemotherapeutic agents.

# Future of Chemotherapeutic Agents (2 of 2)

- Target virulence factors
- Sequester iron, which feeds pathogens
- Antimicrobial peptides produced by various organisms
- Phage therapy
- Bacteriocins: antimicrobial peptides produced by bacteria

# Check Your Understanding-15

## Check Your Understanding

- ✓ What are defensins? (**Hint:** See Chapter 16.)
  20-19